CLINICAL PRACTICE

Vitamin D Insufficiency

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A healthy 61-year-old white woman is concerned about a low vitamin D level detected during an assessment of her skeletal health. Her menopause began at 54 years of age. She has no history of falls, and there is no family history of hip fracture. She takes no medications or supplements. Her height is 157.5 cm (5 ft 2 in.), and her weight 59.1 kg (130 lb). The results of a physical examination are unremarkable, and the findings on laboratory studies are normal. The T score for bone mineral density at the hip is –1.5, and the serum level of 25-hydroxyvitamin D is 21 ng per milliliter (53 nmol per liter). What do you advise?

THE CLINICAL PROBLEM

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N Engl J Med 2011;364:248-54.

An audio version of this article is available at NEJM.org

Whereas frank vitamin D deficiency (serum level of 25-hydroxyvitamin D below 10 ng per milliliter [25 nmol per liter]) has long been recognized as a medical condition characterized by muscle weakness, bone pain, and fragility fractures, vitamin D "insufficiency," characterized as a serum level of 25-hydroxyvitamin D of 10 to 30 ng per milliliter (25 to 75 nmol per liter), without overt clinical symptoms, has recently become a concern on the part of physicians and patients.[1] Increased attention to this new "syndrome" and its potential complications has led to a substantial increase in testing for the metabolite 25-hydroxyvitamin D, the best clinical measure of vitamin D stores. The number of 25-hydroxyvitamin D assays performed by one major reference laboratory increased by 50% in the fourth quarter of 2009 as compared with the same quarter in 2008, and it is expected that several million tests will be performed this year.[2]

The implications of vitamin D levels that are below the normal reference range but not markedly reduced and the value of supplementation are incompletely understood. Vitamin D is critical for skeletal mineralization, and numerous observational studies have linked low levels of 25-hydroxyvitamin D to fractures.[3-7] Therefore it is not surprising that most observational and randomized, placebo-controlled trials concerning vitamin D insufficiency have focused on skeletal health outcomes. In the past several years, attention has turned to nonskeletal effects of vitamin D insufficiency, particularly in relation to cardiovascular disease, diabetes mellitus, cancer, and immune dysfunction.[8-11] This review summarizes the current understanding and uncertainties regarding vitamin D insufficiency and the effects of vitamin D supplementation on health outcomes.

STRATEGIES AND EVIDENCE

DEFINING VITAMIN D INSUFFICIENCY

Interpreting the import of a serum level of 25-hydroxyvitamin D in the "insufficient" range (i.e., 10 to 30 ng per milliliter) is challenging for several reasons. First, most reference laboratories have raised the lower boundary of the normal range to

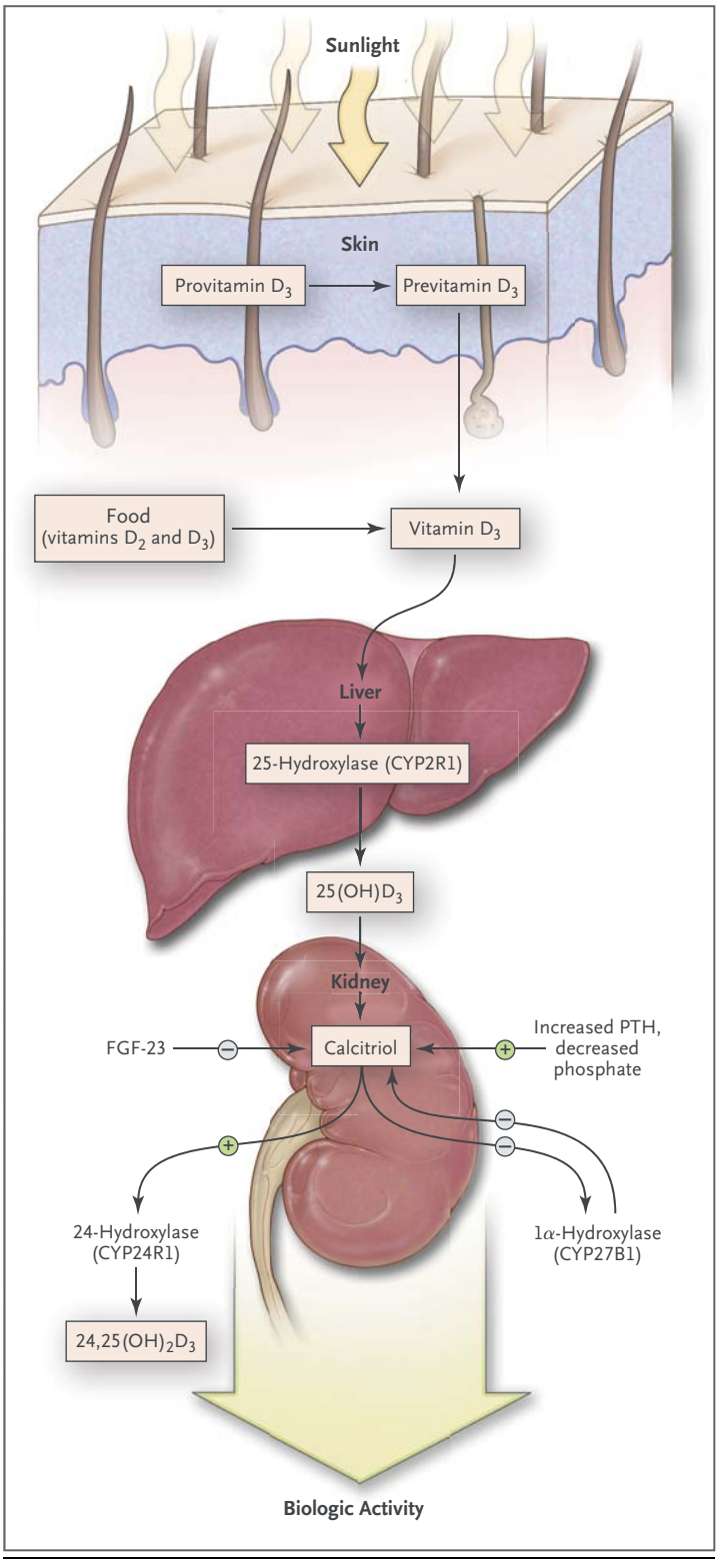

Figure 1. Synthesis and Metabolism of Vitamin D.

Vitamin D is initially generated in the skin from the nonenzymatic conversion of provitamin D_3 to previtamin D_3. Dietary intake of vitamin D is usually relatively limited, since few foods, with the exception of certain kinds of fish, contain sizable amounts; supplements are commonly used. Vitamin D is either stored in adipose tissue or converted in the liver by the enzyme 25-hydroxylase to 25-hydroxyvitamin D_3 (25[OH]D_3), the form that circulates in the highest concentration and reflects solar and dietary exposure. It is converted to the active metabolite, 1,25-dihydroxyvitamin D (1,25$[OH]_2$D), or calcitriol, in the kidney, although other tissues have 1α-hydroxylase enzymatic activity. The synthesis of calcitriol is enhanced (+) by increasing levels of parathyroid hormone (PTH), which rise in response to lower levels of serum calcium. Reduced levels of serum phosphate can also increase (+) the production of calcitriol. Its synthesis is suppressed (–) by the production of fibroblast growth factor 23 (FGF-23), which is secreted by osteocytes in the bone matrix. Calcitriol inhibits the activity of 1α-hydroxylase (CYP27B1) and stimulates the activity of 24-hydroxylase (CYP24R1), an enzyme that promotes production of 24,25$(OH)_2D_3$, a vitamin D product that is not biologically active. In CYP2R1, CYP27B1, and CYP24R1, CYP denotes cytochrome P.

30 ng per milliliter. Second, although there are several ways to measure 25-hydroxyvitamin D (radioimmunoassays, enzyme-linked assays, and liquid chromatography with mass spectrometry), the precision and accuracy of the assays, especially in nonreference laboratories, remain problematic.[12] Third, 25-hydroxyvitamin D levels change with the seasons, exposure to sunlight, and dietary intake. For example, in northern latitudes, serum levels of 25-hydroxyvitamin D decline by 20% from late summer to midwinter, whereas 30 minutes of full-body exposure to the sun during the summer rapidly generates vitamin D. Regular exposure to sunlight (depending on its strength) can increase the serum level of 25-hydroxyvitamin D.[3]

What does a serum 25-hydroxyvitamin D level represent? Vitamin D is produced by the nonenzymatic conversion of provitamin D to previtamin D in the skin during exposure to sunlight emitting ultraviolet radiation in the narrow band of 290 to 315 nm (Fig. 1). Some vitamin D also comes from food sources (between 100 and 200 IU per day). Vitamin D is converted in the liver to 25-hydroxyvitamin D, a partially water-soluble form with a shorter half-life than vitamin D that circulates bound to vitamin D–binding protein. About 40 to 50% of circulating 25-hydroxyvitamin D is derived from skin conversion.[1,3] The active form of vitamin D is 1,25-dihydroxyvitamin D, which is generated primarily in the kidney. It circulates in lower concentrations than

25-hydroxyvitamin D but has much greater affinity for the vitamin D receptor and is biologically more potent. Low levels of 1,25-dihydroxyvitamin D do not reflect low levels of 25-hydroxyvitamin D but result from other causes, most commonly renal insufficiency and less frequently oncogenic osteomalacia.

The serum 25-hydroxyvitamin D level is the best indicator of overall vitamin D status because this measurement reflects total vitamin D from dietary intake and sunlight exposure, as well as the conversion of vitamin D from adipose stores in the liver.[13,14] According to the National Health and Nutrition Evaluation Survey (NHANES), in the United States, the average dietary intake of vitamin D (including supplements) may be as low as 200 IU per day (with differences according to age).[15] Skin-derived synthesis of vitamin D is quite variable, depending on pigmentation, latitude, season, clothing, age, sunscreen use, and local weather conditions. Levels of 25-hydroxyvitamin D are considerably lower among blacks than among whites because of greater pigmentation in blacks. In healthy whites, serum levels of 25-hydroxyvitamin D may vary according to environmental, hormonal, genetic, and nutritional factors.[3,14] The body-mass index (BMI), for example, is inversely related to the serum 25-hydroxyvitamin D level, and obese patients typically have levels in the range of 10 to 20 ng per milliliter (25 to 50 nmol per liter); these differences may be due in part to lower levels of exercise and sunlight exposure in obese persons than lean persons. Several conditions cause very low serum levels of 25-hydroxyvitamin D (i.e., below 10 ng per milliliter), including poor dietary intake of vitamin D coupled with negligible sun exposure; malabsorption due to inflammatory bowel disease, gluten enteropathy, gastric surgery, biliary disease, or intestinal overgrowth; use of antiseizure medications (e.g., phenobarbital or phenytoin); and long-term use of glucocorticoids.[1,3]

Defining a level of serum 25-hydroxyvitamin D as low or insufficient depends on the level that is defined as normal. Previously, according to the World Health Organization, levels below 10 ng per milliliter were considered deficient and levels below 20 ng per milliliter were classified as insufficient.[16] However, with the recent changes in laboratory reference ranges, a normal level is now typically defined as a serum level of 30 to 76 ng per milliliter (75 to 190 nmol per liter). When that range is used, the estimated prevalence of vitamin D insufficiency is as high as 50 to 80% in the general population.[17,18] According to the NHANES for 2005 and 2006, the mean 25-hydroxyvitamin D level among several age groups was 24 ng per milliliter (60 nmol per liter), a level considered to be insufficient according to some standards.[15]

There are two rationales for setting the low end of the normal range for 25-hydroxyvitamin D at 30 ng per milliliter: one, put forward in studies published in the past several years, suggests that levels of parathyroid hormone (PTH) rise when levels of 25-hydroxyvitamin D fall below 30 ng per milliliter[3,13,19]; the other, proposed in earlier studies, suggests that active calcium absorption is optimal when the level of 25-hydroxyvitamin D is 30 ng per milliliter.[20] However, both tenets are now being questioned.[14] Data indicate that the relationship of PTH and 25-hydroxyvitamin D is not curvilinear, and there is substantial variation in PTH levels when 25-hydroxyvitamin D levels are between 20 and 30 ng per milliliter. There is no absolute threshold level of serum 25-hydroxyvitamin D at which PTH levels rise.[13,19] Furthermore, although the information derived from dual isotope analysis is the most accurate measure of calcium absorption, there are too few studies to establish an absolute cutoff for levels of 25-hydroxyvitamin D above which calcium absorption is not enhanced. Generally, peak absorption of calcium occurs at levels between 20 and 30 ng per milliliter.

VITAMIN D AND BONE HEALTH

Although recent attention has focused on the nonskeletal effects of vitamin D, it is well established that vitamin D is critical for bone mineralization.[1,8-11] Therefore, it is not surprising that most studies of vitamin D have assessed outcomes for skeletal health.

Several observational studies of the associations between serum levels of 25-hydroxyvitamin D and skeletal health have had conflicting results. A report from Ottawa on 15 studies (3 prospective cohort studies and 12 case–control studies) concluded that associations between serum 25-hydroxyvitamin D concentrations and fractures, falls, and performance measures (tests of gait, stability, and activity) among postmenopausal women or elderly men were inconsistent.[21] A more recent report from the Agency for Healthcare Research and Quality (AHRQ) and Tufts Medical

Center, analyzing the same observational studies, concluded that there was fair, or reasonable, evidence of an association between lower serum concentrations of 25-hydroxyvitamin D and an increased risk of falls among institutionalized elderly persons.[22]

Randomized, controlled trials of vitamin D supplementation have addressed its effects on skeletal outcomes, but most of these trials involved supplementation with both vitamin D and calcium, making it impossible to separate out the effects attributable specifically to vitamin D. The results of a 2007 meta-analysis of 29 trials of supplementation with both calcium and vitamin D or with calcium alone suggested that daily supplementation with 1200 mg of calcium and at least 800 IU of vitamin D resulted in reduced rates of fracture and a modest increase in bone mineral density, but the relationship between serum 25-hydroxyvitamin D levels and skeletal outcomes was not assessed.[23] A 2009 Cochrane meta-analysis of 10 trials testing the effects of vitamin D supplementation alone and 8 trials testing the effects of vitamin D plus calcium showed no significant relationship between vitamin D supplementation alone and a reduction in the risk of fracture.[24] However, the study confirmed the conclusion of the 2007 meta-analysis that calcium plus vitamin D was marginally effective in reducing the risk of fracture in older persons as compared with no supplementation (odds ratio, 0.89; 95% confidence interval, 0.80 to 0.99).

Despite the observational data suggesting an inverse association between serum levels of 25-hydroxyvitamin D and the risk of falls among institutionalized elderly persons, the evidence is inconsistent, with some studies showing a benefit and others showing no effect of vitamin D supplementation on the risk of fractures or falls in various populations.[22,25] Similarly, a randomized study conducted by the Women's Health Initiative showed a nonsignificant reduction in hip fractures among women receiving a total of 700 IU of vitamin D and more than 2000 mg of calcium per day.[26] However, the high baseline intake of calcium (an average of 1100 to 1200 mg per day) and vitamin D (approximately 300 IU per day) in the placebo group may have limited the ability of the investigators to detect effects of supplementation. Subgroup analyses of women over 60 years of age and of those who adhered to their supplementation regimen showed a significant reduction in hip fractures with supplementation, but these results must be interpreted with caution. Randomized trials of supplementation with vitamin D_2 or D_3 (with daily doses ranging from 400 to 822 IU) published after the AHRQ–Tufts analysis also failed to show significant effects of vitamin D supplementation on the risk of fracture or falls in older populations.[27,28] However, in one of those trials, vitamin D supplementation at a dose of 400 IU daily improved gait speed and reduced body sway.[27]

Several large observational studies have addressed the question of whether there is a threshold level of 25-hydroxyvitamin D below which adverse skeletal outcomes are more likely to occur. In one study of elderly men, levels below 16 ng per milliliter (40 nmol per liter) were associated with a greater risk of fracture, whereas in another study, men with levels below 20 ng per milliliter had greater rates of femoral bone loss than men with higher levels.[29,30] In a longitudinal study, Osteoporotic Fractures in Men (MrOs), older men with serum levels of 25-hydroxyvitamin D that were less than 20 ng per milliliter had a higher risk of hip fracture than men with higher levels.[31] In a prospective study of older women, 25-hydroxyvitamin D levels between 24 and 26 ng per milliliter (60 to 65 nmol per liter) were associated with the lowest risk of hip fracture; no additional risk reduction was noted above that level.[32] However, in a study of older New Zealand women, levels of 25-hydroxyvitamin D below 20 ng per milliliter were not associated with an increased risk of fracture during 5 years of follow-up.[33]

VITAMIN D AND OTHER HEALTH EFFECTS

Observational studies in large cohorts have shown significant associations between low levels of 25-hydroxyvitamin D (i.e., below 20 ng per milliliter) and an increased risk of metabolic, neoplastic, and immune disorders such as type 1 diabetes mellitus and multiple sclerosis.[7-11] The two conditions most often connected with low levels of vitamin D are atherosclerosis and diabetes mellitus.[34-36] For example, a significantly increased risk of type 2 diabetes has been reported among persons with levels of vitamin D that are insufficient (below 30 ng per milliliter), even after adjustment for BMI and percentage of body fat.[8,35] Similarly, another prospective study showed that levels of serum 25-hydroxyvitamin D below 20 ng

per milliliter were associated with an increased risk of cardiovascular disease.[10] However, there are not enough data from large, randomized, controlled trials to assess whether vitamin D supplementation reduces the risk of chronic diseases other than osteoporosis.

AREAS OF UNCERTAINTY

The dynamics of vitamin D storage and reentry into the circulation remain poorly understood, particularly in obese persons.[37] Optimal dosage regimens for vitamin D remain uncertain. In general, for every 100 IU of vitamin D taken in, there is an increase of roughly 1 ng per milliliter (3 nmol per liter) in the serum level of 25-hydroxyvitamin D; the lower the baseline level of 25-hydroxyvitamin D, the greater the rise with vitamin D supplementation. Most trials assessing the association between 25-hydroxyvitamin D levels and the risk of fractures and falls have used daily doses of vitamin D between 400 and 1000 IU. Data are scarce on the effects of long-term supplementation with doses greater than 1000 IU per day. In a recently published randomized, placebo-controlled trial involving elderly persons not living in institutions, those who received an oral dose of 500,000 IU of vitamin D once a year for 3 years had a significantly increased rate of falls and fractures, as compared with those who received placebo, particularly in the first 3 months after dosing.[38] These results suggest that high intermittent doses of vitamin D, as compared with daily doses, may be metabolized and used differently. Finally, data are lacking from large randomized, controlled trials designed to determine whether vitamin D supplementation reduces the risk of other major diseases, such as colon cancer, for which there are observational data suggesting a reduction in risk with supplementation. The ongoing Vitamin D and Omega-3 Trial (VITAL; ClinicalTrials.gov number, NCT01169259), a 5-year, randomized, placebo-controlled trial involving 20,000 U.S. men and women is examining vitamin D supplementation (2000 IU per day), with or without supplementation of n–3 fatty acids, for the primary prevention of cancer and cardiovascular disease.

Toxicity from vitamin D supplementation is rare and consists principally of acute hypercalcemia, which usually results from doses that exceed 10,000 IU per day; associated serum levels of 25-hydroxyvitamin D are well above 150 ng per milliliter (375 nmol per liter).[39] The tolerable upper level of daily vitamin D intake recently set by the Institute of Medicine (IOM) is 4000 IU.[14] The long-term effects of supplementation at doses above 4000 IU per day are not known, and risks cannot be ruled out. Recent observational studies have suggested associations between serum levels of 25-hydroxyvitamin D above 60 ng per milliliter (150 nmol per liter) and increased risks of pancreatic cancer, vascular calcification, and death from any cause,[34,40,41] but the observational nature of these studies precludes an assessment of cause and effect. More longitudinal studies and controlled trials are needed.

Several studies have suggested that vitamin D supplementation may be most effective in reducing fractures and falls in institutionalized elderly persons, in whom serum levels of 25-hydroxyvitamin D are often below 20 ng per milliliter.[42-44] Yet the optimal replacement dose in this population is still not known. A large, long-term, randomized trial is warranted to examine the effects of several different doses of vitamin D on physical performance measures and the incidence of falls and fractures in the institutionalized elderly population.

GUIDELINES FROM PROFESSIONAL SOCIETIES

At an international workshop on vitamin D held in 2007, there was agreement that most of the world's population is not getting an amount of vitamin D sufficient to maintain healthy bone mass and minimize the risk of fracture. The workshop members also agreed that vitamin D insufficiency decreases muscle strength and increases the risk of falls.[45] The recommendation from that group, made on the basis of available observational data, was that the minimum desirable serum level of 25-hydroxyvitamin D is 20 ng per milliliter. Three years later, Osteoporosis Canada issued a report stating that the 25-hydroxyvitamin D level should be at least 30 ng per milliliter and that vitamin D insufficiency should be defined as a level of 10 to 29 ng per milliliter.[46] In 2010, the International Osteoporosis Foundation issued a position statement on vitamin D status, also based on observational data, recommending a target serum level of 25-hydroxyvitamin D of 30 ng per milliliter in all elderly persons and

stating that vitamin D intakes as high as 2000 IU per day may be necessary to attain the recommended level in some persons.[47] In contrast, the IOM report, based on evidence from observational studies and recent randomized trials, suggests that a serum level of 20 ng per milliliter of 25-hydroxyvitamin D would protect 97.5% of the population against adverse skeletal outcomes such as fractures and falls.[14]

CONCLUSIONS AND RECOMMENDATIONS

The woman described in the vignette is a healthy postmenopausal woman with slightly low bone mineral density and a 25-hydroxyvitamin D level of 21 ng per milliliter. Although the laboratory that performed the measurement, and many other laboratories, would label that level as insufficient, she is certainly not deficient in vitamin D. According to the Fracture Risk Assessment Tool (FRAX) developed by the World Health Organization, the probability that she will sustain a hip fracture over the next 10 years is less than 1%. Moreover, she is not at high risk for falls and is unlikely to have osteomalacia.[48] Hence, for patients such as this one, I would recommend an exercise program and a total calcium intake of 1200 mg per day. There remains uncertainty about whether vitamin D supplementation is appropriate for her, and if so, what the dose should be, although the recent IOM guidelines recommend 600 IU daily for a postmenopausal woman who is not at high risk for fractures or falls and 800 IU daily for persons who have a very high risk of osteoporosis or who are older than 70 years of age.[14] I would explain that despite the recent focus in the media on the potential role of vitamin D in reducing the risk of various chronic diseases, this hypothesis requires testing in large, randomized, controlled trials, and vitamin D cannot currently be recommended for the purpose of reducing the risk of heart disease or cancer.

Dr. Rosen reports serving as an unpaid consultant for Lexicon Genetics and serving on the Vitamin D Subcommittee for the IOM, for which he received reimbursement for travel expenses. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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REVIEW ARTICLE

MEDICAL PROGRESS

Vitamin D Deficiency

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N Engl J Med 2007;357:266-81.

Once foods were fortified with vitamin D and rickets appeared to have been conquered, many health care professionals thought the major health problems resulting from vitamin D deficiency had been resolved. However, rickets can be considered the tip of the vitamin D–deficiency iceberg. In fact, vitamin D deficiency remains common in children and adults. In utero and during childhood, vitamin D deficiency can cause growth retardation and skeletal deformities and may increase the risk of hip fracture later in life. Vitamin D deficiency in adults can precipitate or exacerbate osteopenia and osteoporosis, cause osteomalacia and muscle weakness, and increase the risk of fracture.

The discovery that most tissues and cells in the body have a vitamin D receptor and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-dihydroxyvitamin D, has provided new insights into the function of this vitamin. Of great interest is the role it can play in decreasing the risk of many chronic illnesses, including common cancers, autoimmune diseases, infectious diseases, and cardiovascular disease. In this review I consider the nature of vitamin D deficiency, discuss its role in skeletal and nonskeletal health, and suggest strategies for its prevention and treatment.

Sources and Metabolism of Vitamin D

Humans get vitamin D from exposure to sunlight, from their diet, and from dietary supplements (Table 1).[1-4] A diet high in oily fish prevents vitamin D deficiency.[3] Solar ultraviolet B radiation (wavelength, 290 to 315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D_3, which is rapidly converted to vitamin D_3 (Fig. 1).[1] Because any excess previtamin D_3 or vitamin D_3 is destroyed by sunlight (Fig. 1), excessive exposure to sunlight does not cause vitamin D_3 intoxication.[2]

Few foods naturally contain or are fortified with vitamin D. The "D" represents D_2 or D_3 (Fig. 1). Vitamin D_2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, and vitamin D_3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both are used in over-the-counter vitamin D supplements, but the form available by prescription in the United States is vitamin D_2.

Vitamin D from the skin and diet is metabolized in the liver to 25-hydroxyvitamin D (Fig. 1), which is used to determine a patient's vitamin D status[1-4]; 25-hydroxyvitamin D is metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to its active form, 1,25-dihydroxyvitamin D.[1-4] The renal production of 1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels.[1-4] Fibroblast growth factor 23, secreted from the bone, causes the sodium–phosphate cotransporter to be internalized by the cells of the kidney and small intestine and also suppresses 1,25-dihydroxyvitamin D synthesis.[5] The efficiency of the absorption of renal calcium and of intestinal calcium and phosphorus is increased in the presence of 1,25-dihy-

droxyvitamin D (Fig. 1).[2,3,6] It also induces the expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (CYP24), which catabolizes both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D into biologically inactive, water-soluble calcitroic acid.[2-4]

DEFINITION AND PREVALENCE OF VITAMIN D DEFICIENCY

Although there is no consensus on optimal levels of 25-hydroxyvitamin D as measured in serum, vitamin D deficiency is defined by most experts as a 25-hydroxyvitamin D level of less than 20 ng per milliliter (50 nmol per liter).[7-10] 25-Hydroxyvitamin D levels are inversely associated with parathyroid hormone levels until the former reach 30 to 40 ng per milliliter (75 to 100 nmol per liter), at which point parathyroid hormone levels begin to level off (at their nadir).[10-12] Furthermore, intestinal calcium transport increased by 45 to 65% in women when 25-hydroxyvitamin D levels were increased from an average of 20 to 32 ng per milliliter (50 to 80 nmol per liter).[13] Given such data, a level of 25-hydroxyvitamin D of 21 to 29 ng per milliliter (52 to 72 nmol per liter) can be considered to indicate a relative insufficiency of vitamin D, and a level of 30 ng per milliliter or greater can be considered to indicate sufficient vitamin D.[14] Vitamin D intoxication is observed when serum levels of 25-hydroxyvitamin D are greater than 150 ng per milliliter (374 nmol per liter).

With the use of such definitions, it has been estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.[7-12,15-22] According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community (not in nursing homes) are deficient in vitamin D.[7-12,15-22] More than 50% of postmenopausal women taking medication for osteoporosis had suboptimal levels of 25-hydroxyvitamin D — below 30 ng per milliliter (75 nmol per liter).[12,22]

Children and young adults are also potentially at high risk for vitamin D deficiency. For example, 52% of Hispanic and black adolescents in a study in Boston[23] and 48% of white preadolescent girls in a study in Maine[24] had 25-hydroxyvitamin D levels below 20 ng per milliliter. In other studies, at the end of the winter, 42% of 15- to 49-year-old black girls and women throughout the United States had 25-hydroxyvitamin D levels below 20 ng per milliliter,[25] and 32% of healthy students, physicians, and residents at a Boston hospital were found to be vitamin D–deficient, despite drinking a glass of milk and taking a multivitamin daily and eating salmon at least once a week.[26]

In Europe, where very few foods are fortified with vitamin D, children and adults would appear to be at especially high risk.[1,7,11,16-22] People living near the equator who are exposed to sunlight without sun protection have robust levels of 25-hydroxyvitamin D — above 30 ng per milliliter.[27,28] However, even in the sunniest areas, vitamin D deficiency is common when most of the skin is shielded from the sun. In studies in Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon, 30 to 50% of children and adults had 25-hydroxyvitamin D levels under 20 ng per milliliter.[29-32] Also at risk were pregnant and lactating women who were thought to be immune to vitamin D deficiency since they took a daily prenatal multivitamin containing 400 IU of vitamin D (70% took a prenatal vitamin, 90% ate fish, and 93% drank approximately 2.3 glasses of milk per day)[33-35]; 73% of the women and 80% of their infants were vitamin D–deficient (25-hydroxyvitamin D level, <20 ng per milliliter) at the time of birth.[34]

CALCIUM, PHOSPHORUS, AND BONE METABOLISM

Without vitamin D, only 10 to 15% of dietary calcium and about 60% of phosphorus is absorbed.[2-4] The interaction of 1,25-dihydroxyvitamin D with the vitamin D receptor increases the efficiency of intestinal calcium absorption to 30 to 40% and phosphorus absorption to approximately 80% (Fig. 1).[2-4,13]

In one study, serum levels of 25-hydroxyvitamin D were directly related to bone mineral density in white, black, and Mexican-American men and women, with a maximum density achieved when the 25-hydroxyvitamin D level reached 40 ng per milliliter or more.[8] When the level was 30 ng per milliliter or less, there was a significant decrease in intestinal calcium absorption[13] that was associated with increased parathyroid hormone.[10-12] Parathyroid hormone enhances the tubular reabsorption of calcium and stimulates the kidneys to produce 1,25-dihydroxyvitamin D.[2-4,6] Parathyroid hormone also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts (Fig. 1).[1-3] Osteoclasts dissolve the mineralized collagen matrix in bone, causing os-

teopenia and osteoporosis and increasing the risk of fracture.[7,8,11,16-21]

Deficiencies of calcium and vitamin D in utero and in childhood may prevent the maximum deposition of calcium in the skeleton.[36] As vitamin D deficiency progresses, the parathyroid glands are maximally stimulated, causing secondary hyperparathyroidism.[7,9-12] Hypomagnesemia blunts this response, which means that parathyroid hormone levels are often normal when 25-hydroxyvitamin D levels fall below 20 ng per milliliter.[37] Parathyroid hormone increases the metabolism of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which further exacerbates the vitamin D deficiency. Parathyroid hormone also causes phosphaturia, resulting in a low-normal or low serum phosphorus level. Without an adequate calcium–phosphorus product (the value for calcium times the value for serum phosphorus), mineralization of the collagen matrix is diminished, leading to classic signs of rickets in children[1,28] and osteomalacia in adults.[7,38]

Whereas osteoporosis is unassociated with bone pain, osteomalacia has been associated with isolated or generalized bone pain.[39,40] The cause is thought to be hydration of the demineralized gelatin matrix beneath the periosteum; the hydrated matrix pushes outward on the periosteum, causing throbbing, aching pain.[7] Osteomalacia can often be diagnosed by using moderate force to press the thumb on the sternum or anterior tibia, which can elicit bone pain.[7,40] One study showed that 93% of persons 10 to 65 years of age who were admitted to a hospital emergency department with muscle aches and bone pain and who had a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome, and depression, were deficient in vitamin D.[41]

OSTEOPOROSIS AND FRACTURE

Approximately 33% of women 60 to 70 years of age and 66% of those 80 years of age or older have osteoporosis.[16,20] It is estimated that 47% of women and 22% of men 50 years of age or older will sustain an osteoporotic fracture in their remaining lifetime. Chapuy et al.[21] reported that among 3270 elderly French women given 1200 mg of calcium and 800 IU of vitamin D_3 daily for 3 years, the risk of hip fracture was reduced by 43%, and the risk of nonvertebral fracture by 32%. A 58% reduction in nonvertebral fractures was observed in 389 men and women over the age of 65 years who were receiving 700 IU of vitamin D_3 and 500 mg of calcium per day.[42]

A meta-analysis of seven randomized clinical

Figure 1 (facing page). Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone Metabolism.

During exposure to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol in the skin is converted to previtamin D_3, which is immediately converted to vitamin D_3 in a heat-dependent process. Excessive exposure to sunlight degrades previtamin D_3 and vitamin D_3 into inactive photoproducts. Vitamin D_2 and vitamin D_3 from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D (hereafter "D" represents D_2 or D_3) made in the skin or ingested in the diet can be stored in and then released from fat cells. Vitamin D in the circulation is bound to the vitamin D–binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D]. This is the major circulating form of vitamin D that is used by clinicians to determine vitamin D status. (Although most laboratories report the normal range to be 20 to 100 ng per milliliter [50 to 250 nmol per liter], the preferred range is 30 to 60 ng per milliliter [75 to 150 nmol per liter].) This form of vitamin D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1α-hydroxylase (1-OHase) to the biologically active form — 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Serum phosphorus, calcium, fibroblast growth factor 23 (FGF-23), and other factors can either increase (+) or decrease (–) the renal production of 1,25$(OH)_2$D. 1,25$(OH)_2$D decreases its own synthesis through negative feedback and decreases the synthesis and secretion of parathyroid hormone by the parathyroid glands. 1,25$(OH)_2$D increases the expression of 25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25$(OH)_2$D to the water-soluble, biologically inactive calcitroic acid, which is excreted in the bile. 1,25$(OH)_2$D enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor–retinoic acid x-receptor complex (VDR-RXR) to enhance the expression of the epithelial calcium channel (transient receptor potential cation channel, subfamily V, member 6 [TRPV6]) and calbindin 9K, a calcium-binding protein (CaBP). 1,25$(OH)_2$D is recognized by its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor-κB ligand (RANKL). RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood. Adequate calcium (Ca^{2+}) and phosphorus (HPO_4^{2-}) levels promote the mineralization of the skeleton.

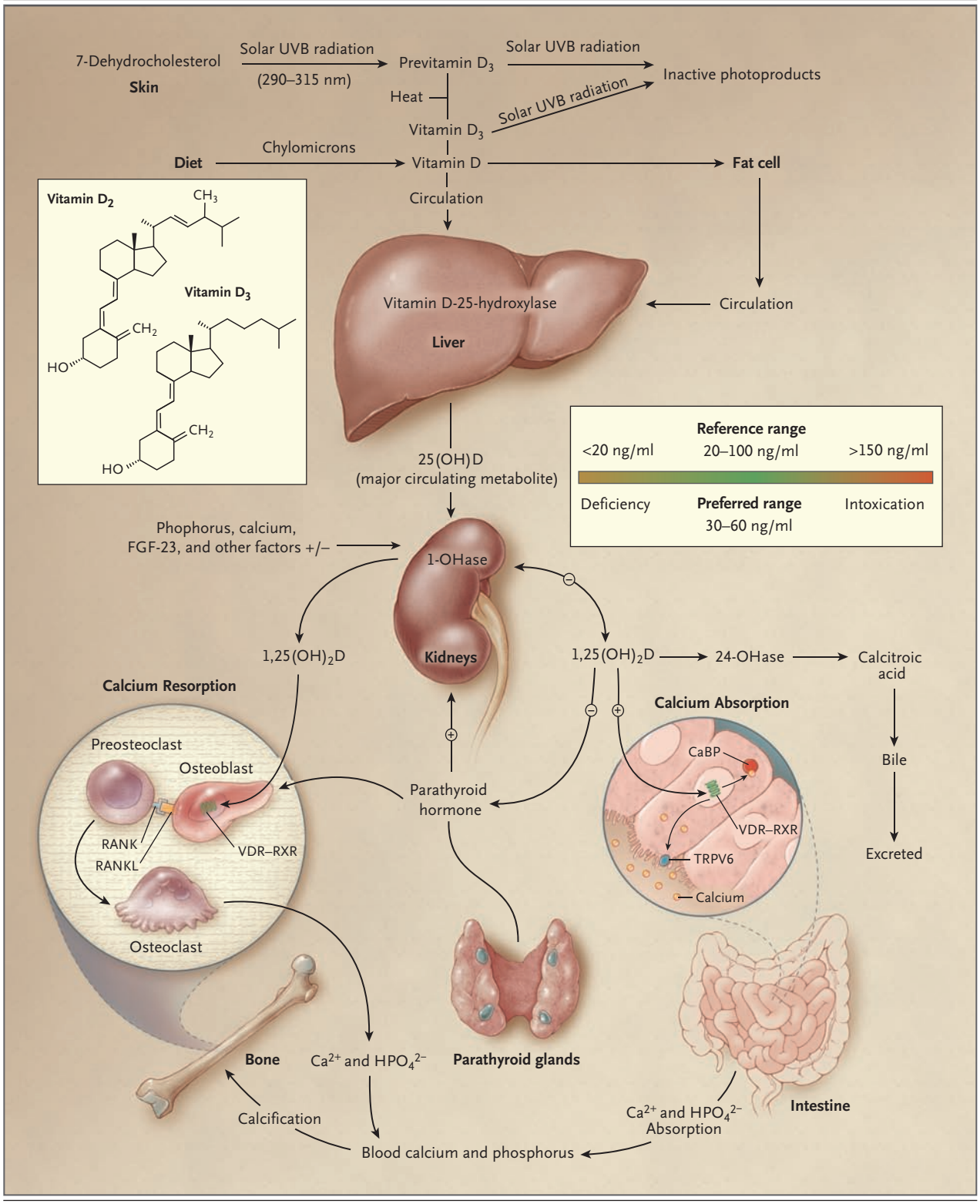

Table 1. Dietary, Supplemental, and Pharmaceutical Sources of Vitamins D_2 and D_3.*

Source	Vitamin D Content
Natural sources	
Salmon	
Fresh, wild (3.5 oz)	About 600–1000 IU of vitamin D_3
Fresh, farmed (3.5 oz)	About 100–250 IU of vitamin D_3 or D_2
Canned (3.5 oz)	About 300–600 IU of vitamin D_3
Sardines, canned (3.5 oz)	About 300 IU of vitamin D_3
Mackerel, canned (3.5 oz)	About 250 IU of vitamin D_3
Tuna, canned (3.6 oz)	About 230 IU of vitamin D_3
Cod liver oil (1 tsp)	About 400–1000 IU of vitamin D_3
Shiitake mushrooms	
Fresh (3.5 oz)	About 100 IU of vitamin D_2
Sun-dried (3.5 oz)	About 1600 IU of vitamin D_2
Egg yolk	About 20 IU of vitamin D_3 or D_2
Exposure to sunlight, ultraviolet B radiation (0.5 minimal erythemal dose)†	About 3000 IU of vitamin D_3
Fortified foods	
Fortified milk	About 100 IU/8 oz, usually vitamin D_3
Fortified orange juice	About 100 IU/8 oz vitamin D_3
Infant formulas	About 100 IU/8 oz vitamin D_3
Fortified yogurts	About 100 IU/8 oz, usually vitamin D_3
Fortified butter	About 50 IU/3.5 oz, usually vitamin D_3
Fortified margarine	About 430 IU/3.5 oz, usually vitamin D_3
Fortified cheeses	About 100 IU/3 oz, usually vitamin D_3
Fortified breakfast cereals	About 100 IU/serving, usually vitamin D_3
Supplements	
Prescription	
Vitamin D_2 (ergocalciferol)	50,000 IU/capsule
Drisdol (vitamin D_2) liquid supplements	8000 IU/ml
Over the counter	
Multivitamin	400 IU vitamin D, D_2, or D_3‡
Vitamin D_3	400, 800, 1000, and 2000 IU

* IU denotes international unit, which equals 25 ng. To convert values from ounces to grams, multiply by 28.3. To convert values from ounces to milliliters, multiply by 29.6.

† About 0.5 minimal erythemal dose of ultraviolet B radiation would be absorbed after an average of 5 to 10 minutes of exposure (depending on the time of day, season, latitude, and skin sensitivity) of the arms and legs to direct sunlight.

‡ When the term used on the product label is vitamin D or calciferol, the product usually contains vitamin D_2; cholecalciferol or vitamin D_3 indicates that the product contains vitamin D_3.

trials that evaluated the risk of fracture in older persons given 400 IU of vitamin D_3 per day revealed little benefit with respect to the risk of either nonvertebral or hip fractures (pooled relative risk of hip fracture, 1.15; 95% confidence interval [CI], 0.88 to 1.50; pooled relative risk of nonvertebral fracture, 1.03; 95% CI, 0.86 to 1.24). In studies using doses of 700 to 800 IU of vitamin D_3 per day, the relative risk of hip fracture was reduced by 26% (pooled relative risk, 0.74; 95% CI, 0.61 to 0.88), and the relative risk of nonvertebral fracture by 23% (pooled relative risk, 0.77; 95% CI, 0.68 to 0.87) with vitamin D_3 as compared with calcium or placebo.[8] A Women's Health Initiative study that compared the effects of 400 IU of vitamin D_3 plus 1000 mg of calcium per day with placebo in more than 36,000 postmenopausal women confirmed these results, reporting an increased risk of kidney stones but no benefit with respect to the risk of hip fracture.

The Women's Health Initiative study also showed that serum levels of 25-hydroxyvitamin D had little effect on the risk of fracture when levels were 26 ng per milliliter (65 nmol per liter) or less. However, women who were most consistent in taking calcium and vitamin D_3 had a 29% reduction in hip fracture.[43] Optimal prevention of both nonvertebral and hip fracture occurred only in trials providing 700 to 800 IU of vitamin D_3 per day in patients whose baseline concentration of 25-hydroxyvitamin D was less than 17 ng per milliliter (42 nmol per liter) and whose mean concentration of 25-hydroxyvitamin D then rose to approximately 40 ng per milliliter.[8]

Evaluation of the exclusive use of calcium or vitamin D_3 (RECORD trial) showed no antifracture efficacy for patients receiving 800 IU of vitamin D_3 per day.[44] However, the mean concentration of 25-hydroxyvitamin D increased from 15.2 ng per milliliter to just 24.8 ng per milliliter (37.9 to 61.9 nmol per liter), which was below the threshold thought to provide antifracture efficacy.[8] Porthouse and colleagues,[45] who evaluated the effect of 800 IU of vitamin D_3 per day on fracture prevention, did not report concentrations of 25-hydroxyvitamin D. Their study had an open design in which participants could have been ingesting an adequate amount of calcium and vitamin D separate from the intervention. This called into question the conclusion that vitamin D supplementation had no antifracture benefit.[8]

MUSCLE STRENGTH AND FALLS

Vitamin D deficiency causes muscle weakness.[1,7,8,28] Skeletal muscles have a vitamin D receptor and may require vitamin D for maximum function.[1,8]

Performance speed and proximal muscle strength were markedly improved when 25-hydroxyvitamin D levels increased from 4 to 16 ng per milliliter (10 to 40 nmol per liter) and continued to improve as the levels increased to more than 40 ng per milliliter (100 nmol per liter).[8] A meta-analysis of five randomized clinical trials (with a total of 1237 subjects) revealed that increased vitamin D intake reduced the risk of falls by 22% (pooled corrected odds ratio, 0.78; 95% CI, 0.64 to 0.92) as compared with only calcium or placebo.[8] The same meta-analysis examined the frequency of falls and suggested that 400 IU of vitamin D_3 per day was not effective in preventing falls, whereas 800 IU of vitamin D_3 per day plus calcium reduced the risk of falls (corrected pooled odds ratio, 0.65; 95% CI, 0.4 to 1.0).[8] In a randomized controlled trial conducted over a 5-month period, nursing home residents receiving 800 IU of vitamin D_2 per day plus calcium had a 72% reduction in the risk of falls as compared with the placebo group (adjusted rate ratio, 0.28%; 95% CI, 0.11 to 0.75).[46]

NONSKELETAL ACTIONS OF VITAMIN D

Brain, prostate, breast, and colon tissues, among others, as well as immune cells have a vitamin D receptor and respond to 1,25-dihydroxyvitamin D, the active form of vitamin D.[1-4,6] In addition, some of these tissues and cells express the enzyme 25-hydroxyvitamin D-1α-hydroxylase.[1-3,6]

Directly or indirectly, 1,25-dihydroxyvitamin D controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis, and angiogenesis.[1,2,47] It decreases cellular proliferation of both normal cells and cancer cells and induces their terminal differentiation.[1-3,6,47] One practical application is the use of 1,25-dihydroxyvitamin D_3 and its active analogues for the treatment of psoriasis.[48,49]

1,25-Dihydroxyvitamin D is also a potent immunomodulator.[2-4,6,50] Monocytes and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis* up-regulate the vitamin D receptor gene and the 25-hydroxyvitamin D-1α-hydroxylase gene. Increased production of 1,25-dihydroxyvitamin D_3 result in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents. When serum levels of 25-hydroxyvitamin D fall below 20 ng per milliliter (50 nmol per liter), the monocyte or macrophage is prevented from initiating this innate immune response, which may explain why black Americans, who are often vitamin D–deficient, are more prone to contracting tuberculosis than are whites, and tend to have a more aggressive form of the disease.[51] 1,25-dihydroxyvitamin D_3 inhibits renin synthesis,[52] increases insulin production,[53] and increases myocardial contractility (Fig. 2).[54]

LATITUDE, VITAMIN D DEFICIENCY, AND CHRONIC DISEASES

CANCER

People living at higher latitudes are at increased risk for Hodgkin's lymphoma as well as colon, pancreatic, prostate, ovarian, breast, and other cancers and are more likely to die from these cancers, as compared with people living at lower latitudes.[55-65] Both prospective and retrospective epidemiologic studies indicate that levels of 25-hydroxyvitamin D below 20 ng per milliliter are associated with a 30 to 50% increased risk of incident colon, prostate, and breast cancer, along with higher mortality from these cancers.[56,59-61,64] An analysis from the Nurses' Health Study cohort (32,826 subjects) showed that the odds ratios for colorectal cancer were inversely associated with median serum levels of 25-hydroxyvitamin D (the odds ratio at 16.2 ng per milliliter [40.4 nmol per liter] was 1.0, and the odds ratio at 39.9 ng per milliliter [99.6 nmol per liter] was 0.53; $P \leq 0.01$). Serum 1,25-dihydroxyvitamin D levels were not associated with colorectal cancer.[61] A prospective study of vitamin D intake and the risk of colorectal cancer in 1954 men showed a direct relationship (with a relative risk of 1.0 when vitamin D intake was 6 to 94 IU per day and a relative risk of 0.53 when the intake was 233 to 652 IU per day, $P<0.05$).[56] Participants in the Women's Health Initiative who at baseline had a 25-hydroxyvitamin D concentration of less than 12 ng per milliliter (30 nmol per liter) had a 253% increase in the risk of colorectal cancer over a follow-up period of 8 years.[62] In a study

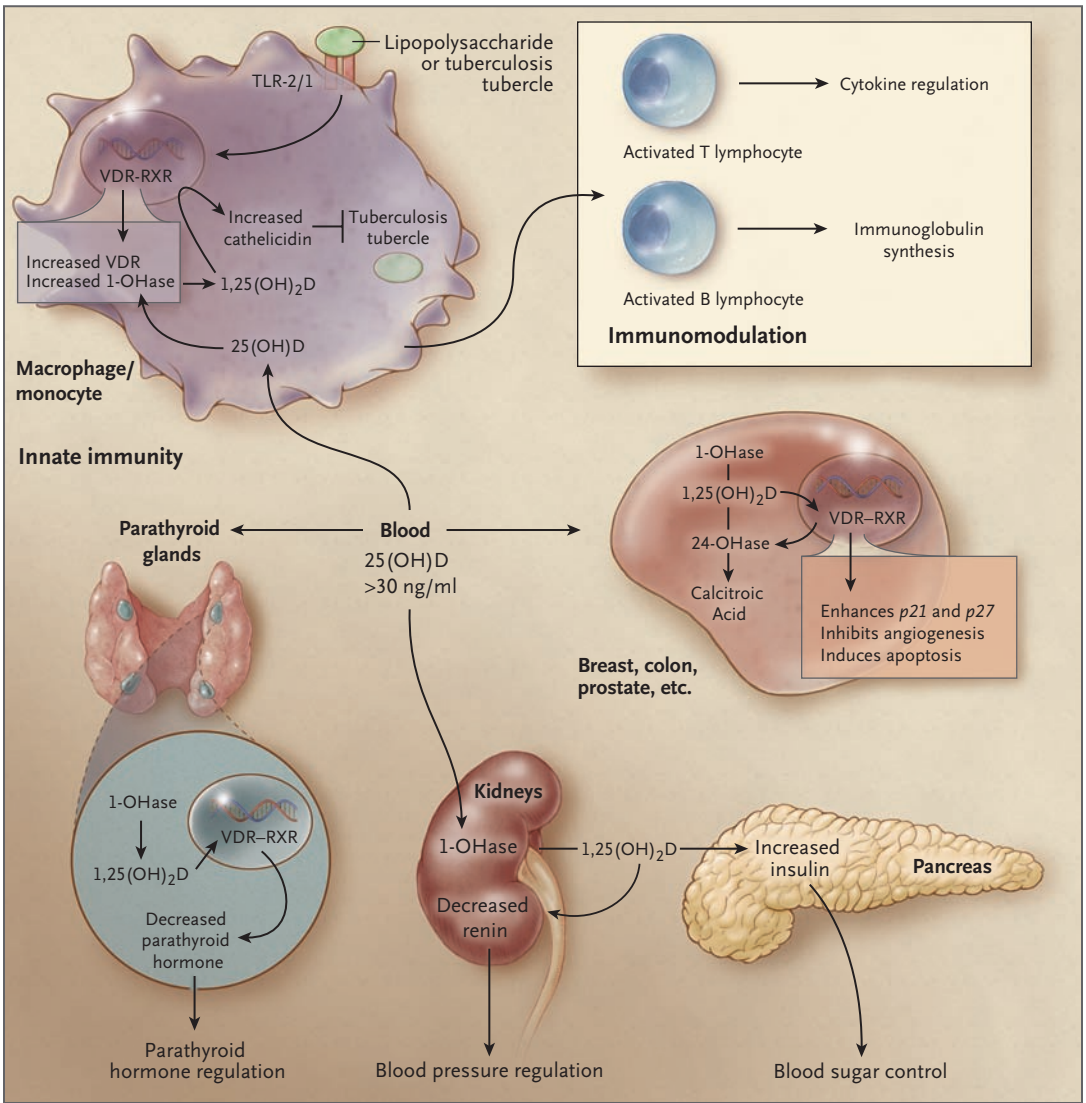

Figure 2. Metabolism of 25-Hydroxyvitamin D to 1,25-Dihydroxyvitamin D for Nonskeletal Functions.

When a macrophage or monocyte is stimulated through its toll-like receptor 2/1 (TLR2/1) by an infectious agent such as *Mycobacterium tuberculosis* or its lipopolysaccharide, the signal up-regulates the expression of vitamin D receptor (VDR) and 25-hydroxyvitamin D-1α-hydroxylase (1-OHase). A 25-hydroxyvitamin D [25(OH)D] level of 30 ng per milliliter (75 nmol per liter) or higher provides adequate substrate for 1-OHase to convert 25(OH)D to its active form, 1,25 dihydroxyvitamin D [$1,25(OH)_2D$]. $1,25(OH)_2D$ travels to the nucleus, where it increases the expression of cathelicidin, a peptide capable of promoting innate immunity and inducing the destruction of infectious agents such as *M. tuberculosis*. It is also likely that the $1,25(OH)_2D$ produced in monocytes or macrophages is released to act locally on activated T lymphocytes, which regulate cytokine synthesis, and activated B lymphocytes, which regulate immunoglobulin synthesis. When the 25(OH)D level is approximately 30 ng per milliliter, the risk of many common cancers is reduced. It is believed that the local production of $1,25(OH)_2D$ in the breast, colon, prostate, and other tissues regulates a variety of genes that control proliferation, including *p21* and *p27*, as well as genes that inhibit angiogenesis and induce differentiation and apoptosis. Once $1,25(OH)_2D$ completes the task of maintaining normal cellular proliferation and differentiation, it induces expression of the enzyme 25-hydroxyvitamin D-24-hydroxylase (24-OHase), which enhances the catabolism of $1,25(OH)_2D$ to the biologically inert calcitroic acid. Thus, locally produced $1,25(OH)_2D$ does not enter the circulation and has no influence on calcium metabolism. The parathyroid glands have 1-OHase activity, and the local production of $1,25(OH)_2D$ inhibits the expression and synthesis of parathyroid hormone. The $1,25(OH)_2D$ produced in the kidney enters the circulation and can down-regulate renin production in the kidney and stimulate insulin secretion in the beta islet cells of the pancreas.

of men with prostate cancer, the disease developed 3 to 5 years later in the men who worked outdoors than in those who worked indoors.[63] Pooled data for 980 women showed that the highest vitamin D intake, as compared with the lowest, correlated with a 50% lower risk of breast cancer.[64] Children and young adults who are exposed to the most sunlight have a 40% reduced risk of non-Hodgkin's lymphoma[65] and a reduced risk of death from malignant melanoma once it develops, as compared with those who have the least exposure to sunlight.[66]

The conundrum here is that since the kidneys tightly regulate the production of 1,25-dihydroxyvitamin D, serum levels do not rise in response to increased exposure to sunlight or increased intake of vitamin D.[1-3] Furthermore, in a vitamin D–insufficient state, 1,25-dihydroxyvitamin D levels are often normal or even elevated.[1,3,6,7] The likely explanation is that colon, prostate, breast, and other tissues express 25-hydroxyvitamin D-1α-hydroxylase and produce 1,25-dihydroxyvitamin D locally to control genes that help to prevent cancer by keeping cellular proliferation and differentiation in check.[1-3,47,56,58] It has been suggested that if a cell becomes malignant, 1,25-dihydroxyvitamin D can induce apoptosis and prevent angiogenesis, thereby reducing the potential for the malignant cell to survive.[2,3,7,67] Once 1,25-dihydroxyvitamin D completes these tasks, it initiates its own destruction by stimulating the *CYP24* gene to produce the inactive calcitroic acid. This guarantees that 1,25-dihydroxyvitamin D does not enter the circulation to influence calcium metabolism (Fig. 1).[1-4] This is a plausible explanation for why increased sun exposure and higher circulating levels of 25-hydroxyvitamin D are associated with a decreased risk of deadly cancers.[56-65]

AUTOIMMUNE DISEASES, OSTEOARTHRITIS, AND DIABETES

Living at higher latitudes increases the risk of type 1 diabetes, multiple sclerosis, and Crohn's disease.[68,69] Living below 35 degrees latitude for the first 10 years of life reduces the risk of multiple sclerosis by approximately 50%.[69,70] Among white men and women, the risk of multiple sclerosis decreased by 41% for every increase of 20 ng per milliliter in 25-hydroxyvitamin D above approximately 24 ng per milliliter (60 nmol per liter) (odds ratio, 0.59; 95% CI, 0.36 to 0.97; P=0.04).[71] Women who ingested more than 400 IU of vitamin D per day had a 42% reduced risk of developing multiple sclerosis.[72] Similar observations have been made for rheumatoid arthritis[73] and osteoarthritis.[74]

Several studies suggest that vitamin D supplementation in children reduces the risk of type 1 diabetes. Increasing vitamin D intake during pregnancy reduces the development of islet autoantibodies in offspring.[53] For 10,366 children in Finland who were given 2000 IU of vitamin D_3 per day during their first year of life and were followed for 31 years, the risk of type 1 diabetes was reduced by approximately 80% (relative risk, 0.22; 95% CI, 0.05 to 0.89).[75] Among children with vitamin D deficiency the risk was increased by approximately 200% (relative risk, 3.0; 95% CI, 1.0 to 9.0). In another study, vitamin D deficiency increased insulin resistance, decreased insulin production, and was associated with the metabolic syndrome.[53] Another study showed that a combined daily intake of 1200 mg of calcium and 800 IU of vitamin D lowered the risk of type 2 diabetes by 33% (relative risk, 0.67; 95% CI, 0.49 to 0.90) as compared with a daily intake of less than 600 mg of calcium and less than 400 IU of vitamin D.[76]

CARDIOVASCULAR DISEASE

Living at higher latitudes increases the risk of hypertension and cardiovascular disease.[54,77] In a study of patients with hypertension who were exposed to ultraviolet B radiation three times a week for 3 months, 25-hydroxyvitamin D levels increased by approximately 180%, and blood pressure became normal (both systolic and diastolic blood pressure reduced by 6 mm Hg).[78] Vitamin D deficiency is associated with congestive heart failure[54] and blood levels of inflammatory factors, including C-reactive protein and interleukin-10.[54,79]

VITAMIN D DEFICIENCY AND OTHER DISORDERS

SCHIZOPHRENIA AND DEPRESSION

Vitamin D deficiency has been linked to an increased incidence of schizophrenia and depression.[80,81] Maintaining vitamin D sufficiency in utero and during early life, to satisfy the vitamin D receptor transcriptional activity in the brain, may be important for brain development as well as for maintenance of mental function later in life.[82]

LUNG FUNCTION AND WHEEZING ILLNESSES

Men and women with a 25-hydroxyvitamin D level above 35 ng per milliliter (87 nmol per liter) had

Table 2. Causes of Vitamin D Deficiency.*

Cause	Effect
Reduced skin synthesis	
Sunscreen use — absorption of UVB radiation by sunscreen[1-3,7,85]	Reduces vitamin D_3 synthesis — SPF 8 by 92.5%, SPF 15 by 99%
Skin pigment — absorption of UVB radiation by melanin[1-3,7,85]	Reduces vitamin D_3 synthesis by as much as 99%
Aging — reduction of 7-dehydrocholesterol in the skin[2,7,85]	Reduces vitamin D_3 synthesis by about 75% in a 70-year-old
Season, latitude, and time of day — number of solar UVB photons reaching the earth depending on zenith angle of the sun (the more oblique the angle, the fewer UVB photons reach the earth)[1-3,85]	Above about 35 degrees north latitude (Atlanta), little or no vitamin D_3 can be produced from November to February
Patients with skin grafts for burns — marked reduction of 7-dehydrocholesterol in the skin	Decreases the amount of vitamin D_3 the skin can produce
Decreased bioavailability	
Malabsorption — reduction in fat absorption, resulting from cystic fibrosis, celiac disease, Whipple's disease, Crohn's disease, bypass surgery, medications that reduce cholesterol absorption, and other causes[86,87]	Impairs the body's ability to absorb vitamin D
Obesity — sequestration of vitamin D in body fat†	Reduces availability of vitamin D
Increased catabolism	
Anticonvulsants, glucocorticoids, HAART (AIDS treatment), and antirejection medications — binding to the steroid and xenobiotic receptor or the pregnane X receptor[1-3,7,88]	Activates the destruction of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D to inactive calcitroic acid
Breast-feeding	
Poor vitamin D content in human milk[1,33,89]	Increases infant risk of vitamin D deficiency when breast milk is sole source of nutrition
Decreased synthesis of 25-hydroxyvitamin D	
Liver failure	
Mild-to-moderate dysfunction	Causes malabsorption of vitamin D, but production of 25-hydroxyvitamin D is possible[2,3,6,7,90]
Dysfunction of 90% or more	Results in inability to make sufficient 25-hydroxyvitamin D
Increased urinary loss of 25-hydroxyvitamin D	
Nephrotic syndrome — loss of 25-hydroxyvitamin D bound to vitamin D–binding protein in urine	Results in substantial loss of 25-hydroxyvitamin D to urine[2,3,6,91]
Decreased synthesis of 1,25-dihydroxyvitamin D	
Chronic kidney disease	
Stages 2 and 3 (estimated glomerular filtration rate, 31 to 89 ml/min/1.73 m^2)	
Hyperphosphatemia increases fibroblast growth factor 23, which decreases 25-hydroxyvitamin D-1α-hydroxylase activity[5,6,91-94]	Causes decreased fractional excretion of phosphorus and decreased serum levels of 1,25-dihydroxyvitamin D
Stages 4 and 5 (estimated glomerular filtration rate <30 ml/min/1.73 m^2)	
Inability to produce adequate amounts of 1,25-dihydroxyvitamin D[2,3,6,91-96]	Causes hypocalcemia, secondary hyperparathyroidism, and renal bone disease

a 176-ml increase in the forced expiratory volume in 1 second.[83] Children of women living in an inner city who had vitamin D deficiency during pregnancy are at increased risk for wheezing illnesses.[84]

CAUSES OF VITAMIN D DEFICIENCY

There are many causes of vitamin D deficiency, including reduced skin synthesis and absorption of vitamin D and acquired and heritable disorders of

Table 2. (Continued.)

Cause	Effect
Heritable disorders — rickets	
Pseudovitamin D deficiency rickets (vitamin D–dependent rickets type 1) — mutation of the renal 25-hydroxyvitamin D-1α-hydroxylase gene (*CYP27B1*)[1-3,97]	Causes reduced or no renal synthesis of 1,25-dihydroxyvitamin D
Vitamin D–resistant rickets (vitamin D–dependent rickets type 2) — mutation of the vitamin D receptor gene[1-3]	Causes partial or complete resistance to 1,25-dihydroxyvitamin D action, resulting in elevated levels of 1,25-dihydroxyvitamin D
Vitamin D–dependent rickets type 3 — overproduction of hormone-responsive-element binding proteins[98]	Prevents the action of 1,25-dihydroxyvitamin D in transcription, causing target-cell resistance and elevated levels of 1,25-dihydroxyvitamin D
Autosomal dominant hypophosphatemic rickets — mutation of the gene for fibroblast growth factor 23, preventing or reducing its breakdown[1-3,5,6,92]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
X-linked hypophosphatemic rickets — mutation of the *PHEX* gene, leading to elevated levels of fibroblast growth factor 23 and other phosphatonins[1-3,5,6,92]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Acquired disorders	
Tumor-induced osteomalacia — tumor secretion of fibroblast growth factor 23 and possibly other phosphatonins[1-3,5,6,92,99]	Causes phosphaturia, decreased intestinal absorption of phosphorus, hypophosphatemia, and decreased renal 25-hydroxyvitamin D-1α-hydroxylase activity, resulting in low-normal or low levels of 1,25-dihydroxyvitamin D
Primary hyperparathyroidism — increase in levels of parathyroid hormone, causing increased metabolism of 25-hydroxyvitamin D to 1,25-hydroxyvitamin D[2,3,6]	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels that are high-normal or elevated
Granulomatous disorders, sarcoidosis, tuberculosis, and other conditions, including some lymphomas — conversion by macrophages of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D[100]	Decreases 25-hydroxyvitamin D levels and increases 1,25-dihydroxyvitamin D levels
Hyperthyroidism — enhanced metabolism of 25-hydroxyvitamin D	Reduces levels of 25-hydroxyvitamin D

* UVB denotes ultraviolet B, SPF sun protection factor, and HAART highly active antiretroviral therapy.
† There is an inverse relationship between the body-mass index and 25-hydroxyvitamin D levels.[2,7,85]

vitamin D metabolism and responsiveness.[2,3,6] Table 2 lists causes and effects of vitamin D deficiency.

VITAMIN D REQUIREMENTS AND TREATMENT STRATEGIES

CHILDREN AND ADULTS

Recommendations from the Institute of Medicine for adequate daily intake of vitamin D are 200 IU for children and adults up to 50 years of age, 400 IU for adults 51 to 70 years of age, and 600 IU for adults 71 years of age or older.[101] However, most experts agree that without adequate sun exposure, children and adults require approximately 800 to 1000 IU per day.[1-3,8,15,16,20,102,103] Children with vitamin D deficiency should be aggressively treated to prevent rickets (Table 3).[1,28,105-107] Since vitamin D_2 is approximately 30% as effective as vitamin D_3 in maintaining serum 25-hydroxyvitamin D levels,[117,118] up to three times as much vitamin D_2 may be required to maintain sufficient levels. A cost-effective method of correcting vitamin D deficiency and maintaining adequate levels is to give patients a 50,000-IU capsule of vitamin D_2 once a week for 8 weeks, followed by 50,000 IU of vitamin D_2 every 2 to 4 weeks thereafter (Table 3).[2,7,9] Alternatively, either 1000 IU of vitamin D_3 per day (available in most pharmacies) or 3000 IU of vitamin D_2 per day is effective.[2,7,102,103] Strategies such as having patients take 100,000 IU of vitamin D_3 once every 3 months have been shown to be effective in maintaining 25-hydroxyvitamin D levels at 20 ng per milliliter or higher and are also effective in reducing the risk of fracture.[119]

BREAST-FED INFANTS AND CHILDREN

Human milk contains little vitamin D (approximately 20 IU per liter), and women who are vitamin D–deficient provide even less to their breast-

Table 3. Strategies to Prevent and Treat Vitamin D Deficiency.*

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Children		
Breast-feeding without vitamin D supplementation[28,33,89,104] — up to 1 yr	400 IU of vitamin D_3/day,[1,28,104] sensible sun exposure,[1] 1000–2000 IU of vitamin D_3/day is safe,[1,2,27,75] maintenance dose is 400–1000 IU of vitamin D_3/day[1,2,104]	200,000 IU of vitamin D_3 every 3 mo,[1,105] 600,000 IU of vitamin D intramuscularly, repeat in 12 wk[106]; 1000–2000 IU of vitamin D_2 or vitamin D_3/day[1,107] with calcium supplementation
Inadequate sun exposure[24,29-31,108] or supplementation,[1,28,104-107] dark skin[23] — 1 through 18 yr	400–1000 IU vitamin D_3/day,[1,104,107] sensible sun exposure, 1000–2000 IU of vitamin D_3/day[1,108] is safe,[1,27,75,104,107] maintenance dose is 400–1000 IU of vitamin D/day[1,75]	50,000 IU of vitamin D_2 every wk for 8 wk[1,9]‡
Adults		
Inadequate sun exposure[7,15] or supplementation,[7-20] decreased 7-dehydrocholesterol in skin because of aging (over 50 yr)[7]	800–1000 IU of vitamin D_3/day,[1-3,8,16,21,42] 50,000 IU of vitamin D_2 every 2 wk or every mo,[7,9] sensible sun exposure[7,15,109,110] or use of tanning bed or other UVB radiation device (e.g., portable Sperti lamp),[111-114] up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU every 2 wk or every mo[7,9]‡	50,000 IU of vitamin D_2 every wk for 8 weeks[9]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Pregnant or lactating (fetal utilization,[33] inadequate sun exposure[33,89] or supplementation[33,89])	1000–2000 IU of vitamin D_3/day,[33,89] 50,000 IU of vitamin D_2 every 2 wk, up to 4000 IU of vitamin D_3/day is safe for 5 mo,[33,89] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[9]‡	50,000 IU vitamin D_2 every wk for 8 wk[115]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Malabsorption syndromes (malabsorption of vitamin D,[2,3,86,87] inadequate sun exposure[2,3,6,7] or supplementation[2,3,6,7])	Adequate exposure to sun or ultraviolet radiation,[7,113] 50,000 IU of vitamin D_2 every day, every other day, or every wk,† up to 10,000 IU of vitamin D_3/day is safe for 5 mo,[27] maintenance dose is 50,000 IU of vitamin D_2 every wk‡	UVB irradiation (tanning bed or portable UVB device, e.g., portable Sperti lamp),[111-114] 50,000 IU of vitamin D_2 every day or every other day‡
Drugs that activate steroid and xenobiotic receptor,[88] and drugs used in transplantation[116]	50,000 IU of vitamin D_2 every other day or every week, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every 2 wk for 8–10 wk, or every wk if 25-hydroxyvitamin D <30 ng/ml‡
Obesity[2,7]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 1 or 2 wk, maintenance dose is 50,000 IU of vitamin D_2 every 1, 2, or 4 wk‡	50,000 IU of vitamin D_2 every wk for 8–12 wk; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Nephrotic syndrome[2,3,6,7,91-94]	1000–2000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 once or twice/wk,[2,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk[2]‡	50,000 IU of vitamin D_2 twice/wk for 8–12 wk[2,94]; repeat for another 8–12 wk if 25-hydroxyvitamin D <30 ng/ml‡
Chronic kidney disease§		
Stages 2 and 3	Control serum phosphate,[6] 1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk,[91,94] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk; may also need to treat with an active vitamin D analog when vitamin D sufficiency is obtained‡	50,000 IU of vitamin D_2 once/wk for 8 wk[91,94]; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml‡
Stages 4 and 5	1000 IU of vitamin D_3/day,[51] 50,000 IU of vitamin D_2 every 2 wk, need to treat with 1,25-dihydroxyvitamin D_3 or active analogue‡	0.25–1.0 μg of 1,25-dihydroxyvitamin D_3 (calcitriol)[2,6,91,93,94] by mouth twice a day or one of the following: 1–2 μg of paricalcitriol IV every 3 days,[6,91,93,94] 0.04–0.1 μg/kg IV every other day initially and can increase to 0.24 μg/kg, 2–4 μg by mouth three times/wk,[6,91,93,94] or doxecalciferol[6,91,93,94] 10–20 μg by mouth three times/wk or 2–6 μg IV three times/wk

Table 3. (Continued.)

Cause of Deficiency†	Preventive and Maintenance Measures to Avoid Deficiency	Treatment of Deficiency
Adults		
Primary or tertiary hyperparathyroidism	800–1000 IU of vitamin D_3/day, 50,000 IU of vitamin D_2 every 2 wk (serum calcium levels will not increase),[115] maintenance dose is 50,000 IU of vitamin D_2 every 2 or 4 wk‡	50,000 IU of vitamin D_2 once a wk for 8 wk; repeat for another 8 wk if 25-hydroxyvitamin D <30 ng/ml
Granulomatous disorders and some lymphomas	400 IU of vitamin D_3/day, maintenance dose is 50,000 IU of vitamin D_2/mo‡	50,000 IU vitamin D_2 once a wk for 4 wk or every 2 to 4 wk, need to keep 25-hydroxyvitamin D between 20 and 30 ng/ml (level above 30 ng/ml can result in hypercalciuria and hypercalcemia)‡

* These recommendations are based on published literature and the author's personal experience. IV denotes intravenously. To convert the values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496.
† For the specific mechanism of deficiency, see Table 2.
‡ The goal is to achieve concentrations of 25-hydroxyvitamin D at about 30 to 60 ng per milliliter. Physicians should use these guidelines in combination with their clinical judgment according to the circumstances.
§ In stages 2 and 3 of chronic kidney disease, the estimated glomerular filtration rate is 31 to 89 ml per minute per 1.73 m^2; in stages 4 and 5, the estimated rate is <30 ml per minute per 1.73 m^2.

fed infants.[33,89] Lactating women given 4000 IU of vitamin D_3 per day not only had an increase in the level of 25-hydroxyvitamin D to more than 30 ng per milliliter but were also able to transfer enough vitamin D_3 into their milk to satisfy an infant's requirement.[89]

In Canada, to prevent vitamin D deficiency, current guidelines recommend that all infants and children receive 400 IU of vitamin D_3 per day (Table 3).[104]

PATIENTS WITH CHRONIC KIDNEY DISEASE

In patients with any stage of chronic kidney disease, 25-hydroxyvitamin D should be measured annually, and the level should be maintained at 30 ng per milliliter or higher, as recommended in the Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation.[6,91,93,94] It is a misconception to assume that patients taking an active vitamin D analogue have sufficient vitamin D; many do not. Levels of 25-hydroxyvitamin D are inversely associated with parathyroid hormone levels, regardless of the degree of chronic renal failure.[2,6,93-96] Parathyroid glands convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which directly inhibits parathyroid hormone expression.[6,93-96,120] Patients with stage 4 or 5 chronic kidney disease and an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area, as well as those requiring dialysis, are unable to make enough 1,25-dihydroxyvitamin D and need to take 1,25-dihydroxyvitamin D_3 or one of its less calcemic analogues to maintain calcium metabolism and to decrease parathyroid hormone levels and the risk of renal bone disease (Table 3).[6,91,93,94]

MALABSORPTION AND MEDICATION

Patients with mild or moderate hepatic failure or intestinal fat-malabsorption syndromes, as well as patients who are taking anticonvulsant medications, glucocorticoids, or other drugs that activate steroid and xenobiotic receptor, require higher doses of vitamin D (Table 3).[7,88] Exposure to sunlight or ultraviolet B radiation from a tanning bed or other ultraviolet B–emitting device is also effective.[7,113,115]

SUNLIGHT AND ARTIFICIAL ULTRAVIOLET B RADIATION

Sensible sun exposure can provide an adequate amount of vitamin D_3, which is stored in body fat and released during the winter, when vitamin D_3 cannot be produced.[7,15,85,108-110] Exposure of arms and legs for 5 to 30 minutes (depending on time of day, season, latitude, and skin pigmentation) between the hours of 10 a.m. and 3 p.m. twice a week is often adequate.[2,7,108-110] Exposure to one minimal erythemal dose while wearing only a bathing suit is equivalent to ingestion of approximately 20,000 IU of vitamin D_2.[1,2,7,85] The skin has a great capacity to make vitamin D_3, even in the elderly, to reduce the risk of fracture.[109-111] Most tanning beds

emit 2 to 6% ultraviolet B radiation and are a recommended source of vitamin D_3 when used in moderation.[111-113,115] Tanners had robust levels of 25-hydroxyvitamin D (approximately 45 ng per milliliter [112 nmol per liter]) at the end of the winter and higher bone density as compared with nontanners (with levels of approximately 18 ng per milliliter [45 nmol per liter]).[112] For patients with fat malabsorption, exposure to a tanning bed for 30 to 50% of the time recommended for tanning (with sunscreen on the face) is an excellent means of treating and preventing vitamin D deficiency (Table 3).[113] This reduces the risk of skin cancers associated with ultraviolet B radiation.

VITAMIN D INTOXICATION

Vitamin D intoxication is extremely rare but can be caused by inadvertent or intentional ingestion of excessively high doses. Doses of more than 50,000 IU per day raise levels of 25-hydroxyvitamin D to more than 150 ng per milliliter (374 nmol per liter) and are associated with hypercalcemia and hyperphosphatemia.[1-3,27,121,122] Doses of 10,000 IU of vitamin D_3 per day for up to 5 months, however, do not cause toxicity.[27] Patients with chronic granulomatous disorders are more sensitive to serum 25-hydroxyvitamin D levels above 30 ng per milliliter because of macrophage production of 1,25-dihydroxyvitamin D, which causes hypercalciuria and hypercalcemia.[1-3,100] In these patients, however, 25-hydroxyvitamin D levels need to be maintained at approximately 20 to 30 ng per milliliter to prevent vitamin D deficiency and secondary hyperparathyroidism (Table 3).[1-3,100]

CONCLUSIONS

Undiagnosed vitamin D deficiency is not uncommon,[1-3,6-20,123] and 25-hydroxyvitamin D is the barometer for vitamin D status. Serum 25-hydroxyvitamin D is not only a predictor of bone health[8] but is also an independent predictor of risk for cancer and other chronic diseases.[8,54,59-64,71-75,83-85] The report that postmenopausal women who increased their vitamin D intake by 1100 IU of vitamin D_3 reduced their relative risk of cancer by 60 to 77% is a compelling reason to be vitamin D–sufficient.[124] Most commercial assays for 25-hydroxyvitamin D are good for detecting vitamin D deficiency. Radioimmunoassays measure total 25-hydroxyvitamin D, which includes levels of both 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3. Some commercial laboratories measure 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3 with liquid chromatography and tandem mass spectroscopy and report the values separately. As long as the combined total is 30 ng per milliliter or more, the patient has sufficient vitamin D.[7,14,27] The 1,25-dihydroxyvitamin D assay should never be used for detecting vitamin D deficiency because levels will be normal or even elevated as a result of secondary hyperparathyroidism. Because the 25-hydroxyvitamin D assay is costly and may not always be available, providing children and adults with approximately at least 800 IU of vitamin D_3 per day or its equivalent should guarantee vitamin D sufficiency unless there are mitigating circumstances (Table 2).

Much evidence suggests that the recommended adequate intakes are actually inadequate and need to be increased to at least 800 IU of vitamin D_3 per day. Unless a person eats oily fish frequently, it is very difficult to obtain that much vitamin D_3 on a daily basis from dietary sources. Excessive exposure to sunlight, especially sunlight that causes sunburn, will increase the risk of skin cancer.[125,126] Thus, sensible sun exposure (or ultraviolet B irradiation) and the use of supplements are needed to fulfill the body's vitamin D requirement.

Supported in part by grants from the National Institutes of Health (M01RR00533 and AR36963) and the UV Foundation.

Dr. Holick reports receiving honoraria from Merck, Eli Lilly, and Procter & Gamble and consulting fees from Quest Diagnostics, Amgen, Novartis, and Procter & Gamble. No other potential conflict of interest relevant to this article was reported.

I thank Dr. Farhad Chimeh for his helpful review of an earlier version of this manuscript and Donna Gendron and Lorrie MacKay for their secretarial assistance.

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